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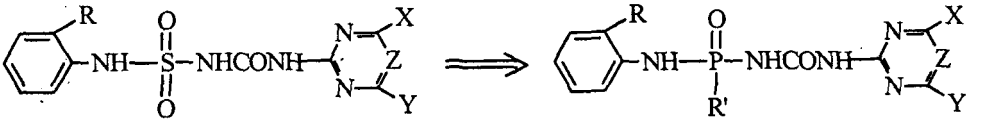
The Synthesis of Novel ALS Inhibitors N-(Substituted Phenyl Alkoxy Phosphonyl)-N'-(4,6-Disubstituted Pyrimidin-2-yl) Ureas

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Sulfonylurea herbicides are a new class of herbicides discovered in the mid-1970's[1], whose mode of action has been established as the inhibition of ALS[2]. Much attention has been focused on this kind of compound, since they have unprecedented use rates, a high degree of selectivity, and excellent environmental safety. Numerous modifications of the structure of this class of herbicides have been reported.

We have taken attention on the similarity between sulfonyl group ($-SO_2-$) and phosphoryl group [-P(O)(OR)-, R=H, CH_3, C_2H_5, etc)]. Their close homolgy in terms of size, bond angle, bond length and configuration suggest that they have good isosterism. Recently, the literatures[3, 4] indicated that sulfonyl group was a bioisostere of the phosphoryl group and useful in bioisosteric replacement of the phosphoryl group.

In order to search new kinds of herbicides, recently we have reported the design and synthesis of several novel ALS inhibitors phosphorylurea compounds **(B-D)** by replacing sulfonyl group ($-SO_2-$) in sulfonylureas **A** with the phosphoryl group [5, 6]. The results in these reports indicated that the phosphoryl group was likely to be an excellent bioisostere of sulfonyl moiety in the sulfonylurea molecule.

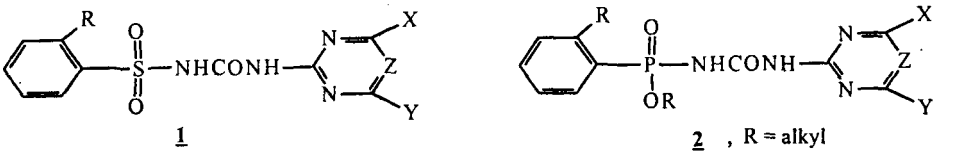


A

B: R' = OH;
C: R' = OR", R" = alkyl;
D: R' = NHR", R" = alkyl.

Therefore, we expected to modify the structures of the other kinds of sulfonylurea herbicides in view of the isosterism of sulfonyl group($-SO_2-$) and phosphoryl group[-P(O)(OR)-, R=H, CH_3, C_2H_5, etc] to develop new ALS inhibitors.

In this paper we report the design and synthesis of another new kind of phosphorylurea compound **2** by replacing sulfonyl group($-SO_2-$) in the related parent compound **1**with -P(O)(OH)-group. Compound **1** is a family of sulfonylurea compounds having excellent herbicidal activity.

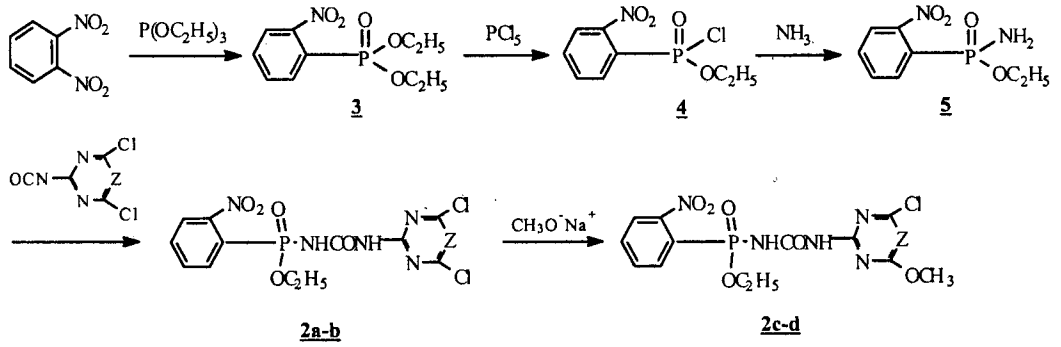


1 2 , R = alkyl

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The synthetic method is shown in Scheme. At first, the material o-nitro phenyl O,O-diethyl phosphonate **3** was synthesized by Arbuzov arrangement of o-dinitro benzene with $P(OC_2H_5)_3$. And then compounds **3** was treated with PCl_5 and with NH_3 gas to give o-nitro phenyl ethoxyl phosphonamide **5**. Compound **5** was treated with 4,6-dichloro-2-pyrimidinyl isocyanate to obtain N-(o-nitro phenyl ethoxyl phosphonyl)-N'-(4, 6-dichloro pyrimidin-2-yl) ureas ($\mathbf{2}_{a\text{-}b}$), which was treated with $CH_3O^-Na^+$ to give N-(o-nitro phenyl ethoxyl phosphonyl)-N'-(4-chloro-6-methoxy pyrimidin-2-yl) ureas ($\mathbf{2}_{c\text{-}d}$). Compounds $\mathbf{2}_{a\text{-}d}$ were characterized by elementary analysis, ^1H NMR, IR and MS.

Scheme:



(2a, 2c: Z = CH; 2b, 2d: Z = N)

We expected to treat compounds $\mathbf{2}_{c\text{-}d}$ with 2 equivalents $NaOCH_3$ to prepare N-(o-nitro phenyl ethoxyl phosphonyl)-N'-(4,6-dimethoxy pyrimidin-2-yl) ureas. But, the replacement of the second Cl atom in pyrimidinyl ring is more difficult than that of the first Cl atom. By enhancing the reaction temperature and the concentration of base we wished to finish the replacement of the second Cl atom. However, the higher temperature and base concentration resulted in the cleavage of P — N bond to give N-(4, 6-dimethoxy pyrimidinyl-2-yl) urea .

The enzyme test in vitro was used to research ALS-inhibition activity of compounds **2.** ALS was partly purified from Chlorosis seedlings of Pea (Pisum sativum L.)[2]. Acetolactate was determined as described by T. B. Ray[2]. The results of the bioassays showed that compounds **2** could reduce the level of acetolactate synthesized and had excellect ALS-inhibition activity. At the concentration of 50ppm or 100ppm the inhibiting effects of compounds **2** were equal to or more than that of DPX — 4189 which is a commercialized herbicide that has high potent ALS-inhibition activity. These results indicated that compounds **2** were a novel class of ALS inhibitors.

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